REMARKS

Examiner has determined that the previous original claims 18-24 and 26-32 are in condition for allowance.

The Examiner rejected claims 1- 17, 25, 33 and 34.

Claims 1-17, 25 ands 33 were stated as being indefinite for falling to particularly point out and distinctly claim the subject matter which applicant regards as the invention. They are amended accordingly.

Claims 1, 11 and 14 were stated as indefinite in the use of "improved" and "longer". Accordingly, these claims are amended to eliminate the indefinite nature in the previous claims 1, 11 and 14.

The Examiner rejected the claims 6 and 7 were rejected due to indefinite in that it did not point out which drug compositions "are made as separate or in combination thereof". Accordingly, they are also amended.

Claim 25 was rejected due to "indefinite in that it refers to prostatic implantation. The reference to prostate was a typographic error. It is amended to correct these deficiencies.

Claim 33 was rejected due to the use of the term "lesser-cost" and "more convenient" which could not be quantified. It is amended to correct those deficiencies.

Claim 34 was rejected due to it "was not described in the specification in such a way as to enable one skilled in art to which it pertains, or with which it is most nearly connected, to make and or use the invention".

It was described in the specification, page 2, lines 18-22 with citations from the textbook of Cancer, Principles and Practice of Oncology, 6th Edition, Volume 1 with 5 references. Copy of this page from this textbook along with its cited reference pages are enclosed. I hope that it will clarify the objections raised against Claim 34. Efforts on chemoprevention of breast cancer is well known to those skilled in the art and advantages of one implant in every five years and at a fraction of the cost for such present treatment will be greatly appreciated by those skilled in the art. Claim 34 is further amended to correct its deficiencies.

Revised Claims:

Former rejected claims No. 1-17 have amended and changed to claim No. 35- 51 in the revised claims.

Original claims 18-24 and 26-32 with no amendments and change in numbering are incorporated herein as such. Examiner has determined that the previous original claims 18-24 and 26-32 are in condition for allowance.

The former Claim 25, 33 and 34 have amended and changed to claim No Claims 52, 53 and 54 in the revised claims.

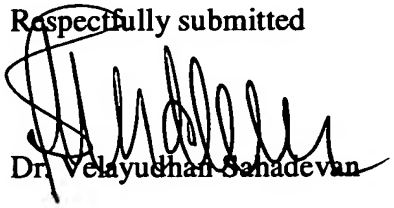
CONCLUSION

The applicant respectfully petitions for Revival of this Patent Application under the Provisions of Unintentional Delay.

All of the stated grounds for rejection and objection have been properly corrected. The applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn. Applicant believes that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the applicant at 304-252-9510.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted



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Hormone Study[11] are the most frequently used. The Gail model, which calculates a woman's risk of developing breast cancer based on age at menarche, age at first live birth, number of previous breast biopsies, the presence or absence of atypical hyperplasia, and the number of first-degree female relatives with breast cancer, has been used in the NSABP breast cancer prevention trials. Efforts to validate the Gail model in different settings have produced variable results. In the Nurses' Health Study cohort, the Gail model was found to overestimate breast cancer risk,[102] although, in other settings, it has proven to be more accurate.[103] In the NSABP prevention trial, the Gail model performed extremely well, with a ratio of observed to predicted cancers in study participants of 1.03 (95% confidence interval, 0.88 to 1.22).[104] In general, the Gail model is thought to underestimate risk in women with strong family histories, at least in part because it only incorporates a family history in first-degree relatives. The Claus model, on the other hand, takes into account both first- and second-degree relatives, although it does not include other risk factors. Not surprisingly, the numeric assessments produced by different models may produce discordant estimates.[105] The widespread use of the Gail model as part of the NSABP prevention trials has led to its general acceptance in clinical practice. In communicating model-based estimates to high-risk women, the limitations of these models should be emphasized. Clinicians should also be aware that women who are anxious about their breast cancer risk may continue to overestimate their risk of developing the disease even after receiving individualized counseling.[7]

Although there is extensive literature on breast cancer screening in the general population, there are few data available on which to base screening recommendations in women with inherited susceptibility genes or other factors that markedly increase breast cancer risk. For high-risk women over the age of 40, annual mammography is recommended.[106] The area of greatest controversy is in screening women under the age of 40. An expert panel has recommended that women with an inherited susceptibility gene should perform monthly breast self-examinations, undergo a clinical breast examination once or twice a year, and have annual mammograms beginning between the ages of 25 and 35.[107] The role of more frequent mammograms (i.e., twice annually), digital mammography, or magnetic resonance imaging (MRI) is uncertain. Ongoing studies are addressing these issues.

BREAST CANCER PREVENTION

The identification of risk factors associated with the development of breast cancer has led to an effort to prevent breast cancer in women at increased risk. Numerous strategies have been considered, including risk factor modification, lifestyle alteration, drug therapy, and prophylactic surgery. Only preliminary evidence suggests that behavioral approaches can be used to alter breast cancer risk,[86,108] and, unfortunately, most of the known risk factors for breast cancer are not easily modifiable. Few women would be willing to modify the age at which they have a first pregnancy in an effort to lower breast cancer risk. While early menopause may be associated with lower breast cancer risk, there are adverse psychological and physical consequences of premature menopause. Some investigators have attempted to alter a woman's natural hormonal milieu to lower breast cancer risk, and it is possible that such approaches might have future promise.[109] To date, however, most efforts to lower a woman's risk of developing breast cancer have focused on pharmacologic interventions.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Adjuvant trials of tamoxifen have demonstrated clear reductions in the development of contralateral breast cancers in women treated with tamoxifen.[110] These data, as well as preclinical evidence supporting a role for tamoxifen in breast cancer prevention,[111,112] led to the development of the NSABP's Breast Cancer Prevention Trial and to various studies in Europe.

The NSABP trial, known as P-1, randomized over 13,000 patients to either tamoxifen for 5 years or to a placebo.[113] To be eligible, women 35 years of age or older had to have at least a 1.66% chance of developing breast cancer over the ensuing 5 years based on the Gail model. Because of the elevated risk associated with age, any woman over the age of 60 was eligible for the trial. Overall, women randomized to 5 years of tamoxifen experienced a 49% decrease in invasive breast cancer, with similar risk reduction seen in women both younger than 50 and older than 50. The benefits of tamoxifen were seen across all patient subgroups (Table 37.2-3) and were highly statistically significant. Despite the high level of statistical significance, the absolute benefit from tamoxifen is of relatively small magnitude, even if one also considers the cases of DCIS prevented by tamoxifen (69 cases in the placebo arm and 35 in women on tamoxifen). To date, the benefit seen with tamox-

TABLE 37.2-3. Incidence of Invasive Breast Cancer in Women Participating in P-1

	Placebo		*Tamoxifen*		*Risk Ratio (95% Confidence Interval)*
	No. of Cases	Annual Rate per 1000 Women	No. of Cases	Annual Rate per 1000 Women	
All women (n = 13,388)	175	6.76	89	3.43	0.51 (0.39–0.66)
Women younger than 50 y (n = 5177)	68	6.70	38	3.77	0.56 (0.37–0.85)
Women 50 to 59 y (n = 4048)	50	6.28	25	3.10	0.49 (0.29–0.81)
Women 60 y or older (n = 3950)	57	7.73	26	3.33	0.45 (0.27–0.74)
Women with history of lobular carcinoma *in situ* (n = 826)	18	12.99	8	5.69	0.44 (0.16–1.06)
Women with history of atypical hyperplasia (n = 1193)	23	10.11	3	1.43	0.14 (0.03–0.47)

(Adapted from ref. 113.)

ifen only applies to the prevention of estrogen receptor (ER)–positive cancers; in P-1, there was no reduction in the risk of ER-negative cancers. While there is reason to believe that the beneficial effects of tamoxifen may extend beyond 5 years,[110] it is unknown to what degree a 5-year course of tamoxifen affects a woman's lifetime risk of developing breast cancer.

The benefits associated with tamoxifen must also be balanced against the potential risks, in terms of both serious toxicities and adverse consequences with respect to quality of life.[113,114] Increases in both endometrial cancer and thromboembolic events were seen in women on tamoxifen, although more commonly in older women (50 and older) than their younger counterparts. Based on these findings, it is thought that tamoxifen may be most beneficial in younger women with an elevated risk of developing breast cancer.[115]

The findings from NSABP P-1 must also be considered in light of two European studies evaluating tamoxifen.[116,117] Both the Royal Marsden Hospital chemoprevention trial and the Italian prevention trial failed to demonstrate a protective effect of tamoxifen. The studies were considerably smaller than P-1 (2494 in the Royal Marsden trial and a total of 5408 in the Italian), and a number of explanations have been offered to explain the negative results. The Royal Marsden trial, for example, may have included a substantial number of women from families with BRCA1 and BRCA2 mutations, and the Italian study results could have been compromised by poor compliance with the study medication. Nevertheless, the European findings provide a sobering counterpoint to the P-1 study. These results, as well as recognition of the limitations of what has been learned from P-1, underscore the need for further research in this area. At present, the need to individualize decision making about tamoxifen in the prevention setting cannot be overemphasized.

Raloxifene, another selective ER modulator, has also been shown to lower the risk of developing invasive breast cancer. In a randomized trial in postmenopausal women with osteoporosis, two doses of raloxifene (60 or 120 mg) were compared with placebo. Treatment with raloxifene not only led to an improvement in bone density and fracture risk, but also appeared to prevent breast cancer.[118,119] Among 5129 women randomized to raloxifene, there were a total of 13 cases of breast cancer, compared with 27 cases among 2576 who were assigned to placebo (relative risk, 0.24; 95% confidence interval, 0.13 to 0.44). Like tamoxifen, raloxifene increased the risk of thromboembolic disease (relative risk, 3.1; 95% confidence interval, 1.5 to 6.2) but did not appear to increase the risk of endometrial cancer. The follow-up of patients on the trial was relatively short (median, 40 months), and women participating in the trial were generally not at increased risk of developing breast cancer (apart from the increased risk associated with increasing age). The NSABP is now conducting a second-generation prevention trial (P-2) in which tamoxifen and raloxifene are being compared directly in postmenopausal women who are at increased risk of developing breast cancer. Until the results of that trial or additional data are available, the routine use of raloxifene to lower a woman's risk of developing breast cancer cannot be recommended.[120,121]

OTHER PHARMACOLOGIC AGENTS TO LOWER BREAST CANCER RISK

Ongoing trials are evaluating a wide range of other agents to lower a woman's risk of developing breast cancer. A randomized Italian study indicated that fenretinide, a differentiating agent in the retinoid family, lowers the risk of contralateral cancers.[122] Unfortunately, symptomatic nyctalopia is a problem for approximately 10% of patients taking this agent.[123] A U.S. Intergroup trial comparing tamoxifen plus placebo versus tamoxifen plus N-(4-hydroxyphenyl) Retinamide was stopped prematurely, making it unlikely that there will be a definitive answer as to whether N-(4-hydroxyphenyl) Retinamide plays a role in a woman's risk of developing breast cancer. Trials involving other differentiating agents, aromatase inhibitors, and vaccines are ongoing, but it is unlikely that there will be any commercially available agent to lower breast cancer risk in the next several years.

PROPHYLACTIC MASTECTOMY

For years it has been assumed that prophylactic mastectomy would lower a woman's risk of developing breast cancer. Since a small amount of breast tissue remains following mastectomy, the level of protection was debated. In a retrospective but rigorously conducted analysis at the Mayo Clinic, Hartmann et al. have demonstrated a 90% reduction in breast cancer risk as a result of prophylactic mastectomy.[124] Most women and their physicians consider prophylactic mastectomy to be an extreme procedure[125]; however, for certain high-risk women, such as those with an inherited genetic predisposition, it is currently an option. Modeling studies have demonstrated that prophylactic mastectomy in women with BRCA1 mutations may result in a modest improvement in survival.[126,127] The decision to proceed with prophylactic surgery should be considered carefully. Unlike many other choices that high-risk women may face, this is one that is irreversible and should not be made without carefully considering all the available options. Women who are considering prophylactic mastectomy with reconstruction should also recognize the potential short- and long-term complications associated with breast reconstruction (see Breast Reconstruction, later in this chapter).

BIOPSY TECHNIQUES FOR SUSPICIOUS BREAST LESIONS

In this section, the various techniques employed to biopsy suspicious palpable and mammographic breast lesions are described. The major techniques used to diagnose palpable breast masses are fine-needle aspiration (FNA), core-cutting needle biopsy, and excisional biopsy. (Incisional biopsy is occasionally used to diagnose large breast masses, but this technique has largely been replaced by the less invasive aspiration or core biopsy.) The advantages and disadvantages of the three techniques are listed in Table 37.2-4. Both FNA and core biopsy are office procedures. Excisional biopsy, with rare exceptions, is an outpatient procedure that can be done using local anesthesia.

The main issue surrounding the use of FNA is the risk of false-negative results. Large series of FNA have demonstrated a sensitivity of 87%, an incidence of insufficient specimens ranging from 4% to 13%, and a false-negative rate of 4.0% to 9.6%.[128–130] Fibrotic tumors, infiltrating lobular, tubular, and cribriform histologies, and physician inexperience have all been found to be sources of false-negative aspirate results.[128,131,132]